Phase 1 First-In-Human Study of KSI-301: A Novel Anti-VEGF Antibody Biopolymer Conjugate With Extended Durability

Diana V. Do, MD
Professor of Ophthalmology
Byers Eye Institute, Stanford University School of Medicine

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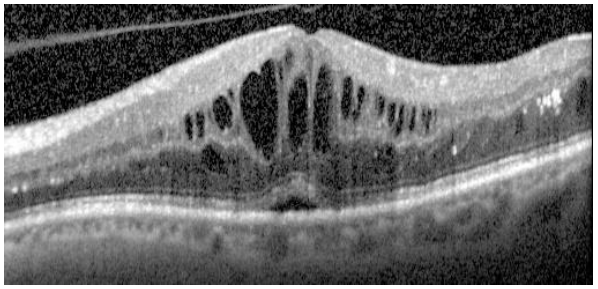
  - Santen

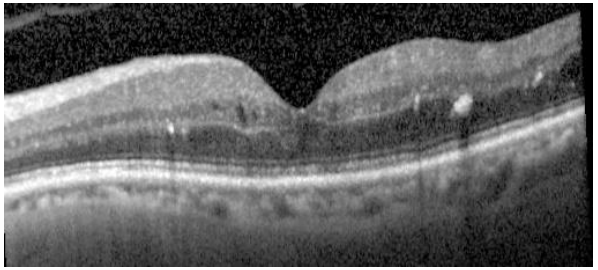
Key Points

- **KSI-301** is a novel **Antibody Biopolymer Conjugate** built on Kodiak's ABC Platform
- Intravitreal KSI-301 inhibits VEGF with **enhanced durability, tissue bioavailability, biocompatibility, and stability**
- Phase 1a single ascending dose study results:
  - Well-tolerated at all dose levels
  - **Rapid-onset, high-magnitude** BCVA gains and OCT retinal thickness reductions, with **improvements sustained to 12 weeks**
- Objective: first line agent for both induction and maintenance therapy of VEGF-mediated retinal vascular diseases

Baseline



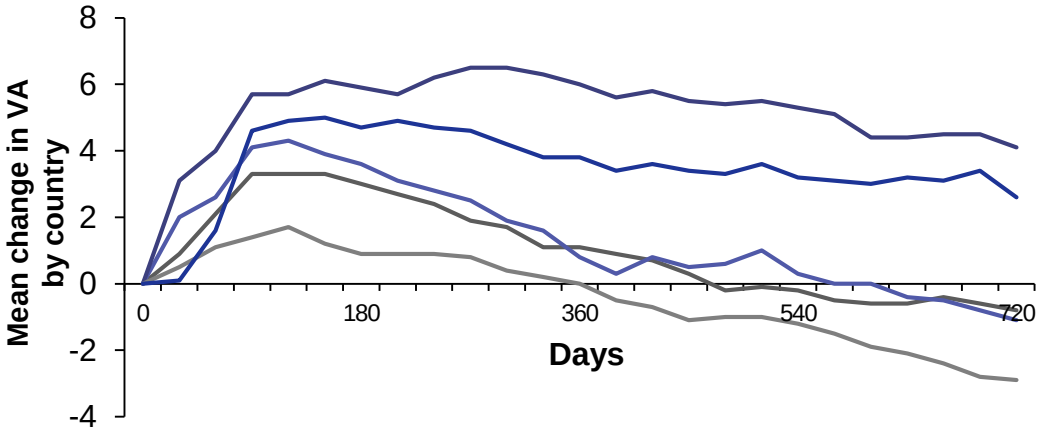
KSI-301 (5mg) Single Dose



Week 12

Real-world outcomes emphasize the **limitations** of current anti-VEGF therapies

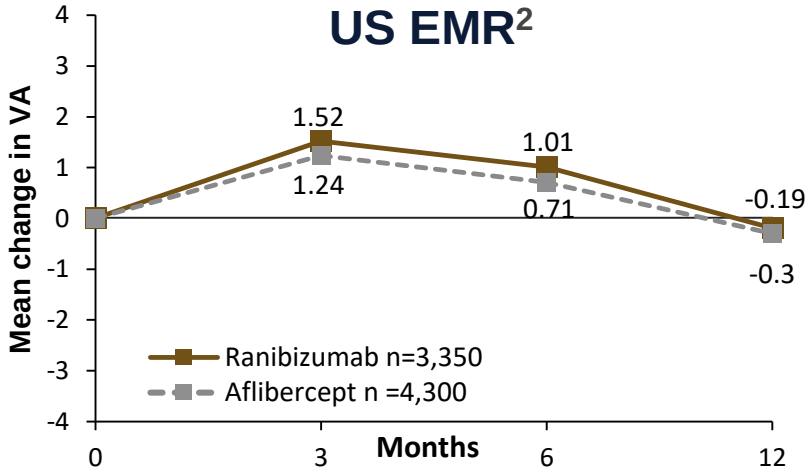
Europe[1]



	Number of injections in 2 years
UK	**9.0**
Netherlands	**8.7**
Germany	**5.6**
France	**6.3**
Italy	**5.2**

Without high intensity treatment, **gradual VA loss** can begin after only 3 months of therapy

US EMR[2]



Mean (±SD) injections at Month 12

Ranibizumab:
6.7 (2.5)
Aflibercept:
7.0 (2.4)

Minimal visual gains are achieved in real-world practice

Patients and physicians need VEGF inhibitors with **extended durability**

1. The AURA Study, adapted from Holz FG et al. Br J Ophthalmol 2015; 99 (2): 220–226.
2. Adapted from Lotery A, et al. Eye (Lond). 2017 Dec;31(12):1697-1706.

EMR= Electronic Medical Records

Designer medicines
to **solve the real-world effectiveness problem**

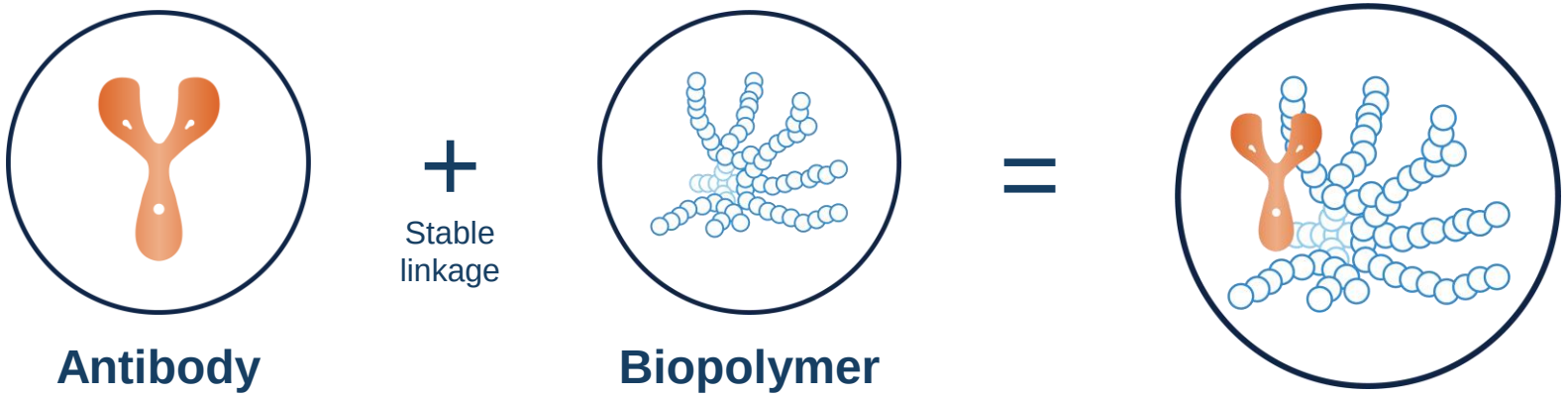
KSI-301 is an antibody biopolymer conjugate intended to be

Same where it matters

- Clinically proven target: VEGF
- Antibody-based biologic
- Intravitreal injection
- Optically clear solution
- No ocular residues

Different where it matters

- Designed-in ocular durability
- Fast systemic clearance
- Improved bioavailability
- Improved biocompatibility
- Improved stability



Antibody

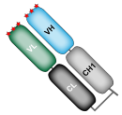
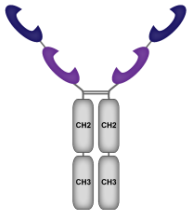
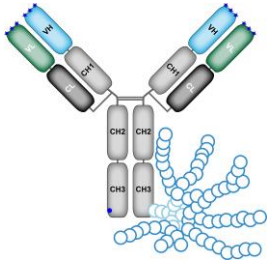
IgG1 with inert immune effector function

Biopolymer

Optically clear, high molecular weight phosphorylcholine polymer

ABC Platform Medicines

KSI-301 bioconjugate **optimizes** both **size and formulation strength** to improve durability

Drug/Candidate:	Brolucizumab	Ranibizumab	Aflibercept	KSI-301
Molecule type	Single-chain Antibody fragment	Antibody fragment	Recombinant fusion protein	**Antibody Biopolymer Conjugate (ABC)**
Molecular structure				
Molecular weight	26 kDa	48 kDa	115 kDa	**950 kDa**
Clinical dose	6 mg	0.3-0.5 mg	2 mg	**5 mg** (by weight of antibody)
Equivalent molar dose	22	1	2	**7**
Equivalent ocular PK	<1	1	1.5	**4**
Equivalent ocular concentration at 3 months	10	1	1,000	**1,000,000**

Equivalent values are showed as fold changes relative to Ranibizumab.

KSI-301 **bioconjugate is more potent** in vitro than unconjugated anti-VEGFs

In vitro assays demonstrate KSI-301 bioconjugate has a **deeper potency** compared to bevacizumab, ranibizumab, and aflibercept because of the special nature of its phosphorylcholine biopolymer

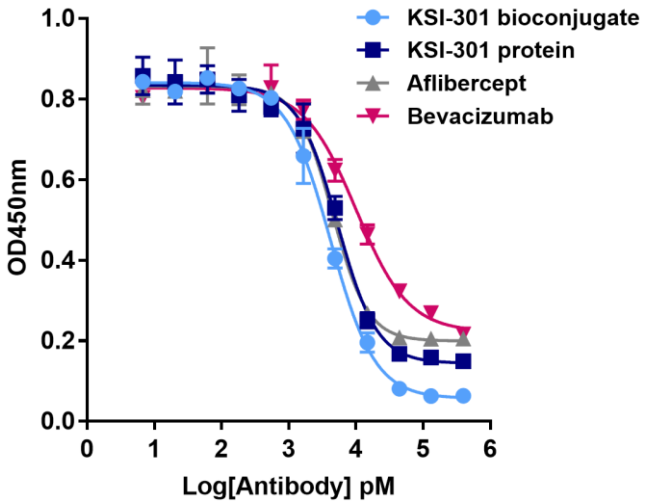
Binding affinity of KSI-301 to VEGF-A

	KinExA (37˚C)
K_{on} (M)	2.69×10^{5}
K_{off} (M)	1.82×10^{-6}
K_D (pM)	**6.75**

KSI-301 has high binding affinity to VEGF

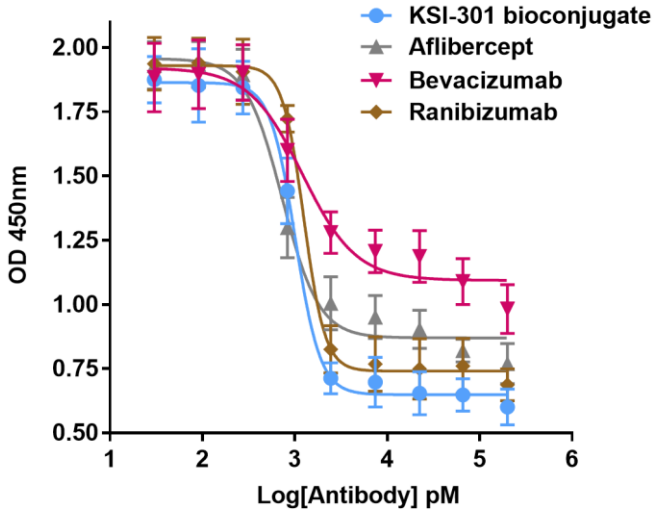
Biochemical assay

Anti-VEGF inhibition of VEGF: VEGFR binding



Primary human retinal cell-based assay

Anti-VEGF inhibition of HRMVEC proliferation

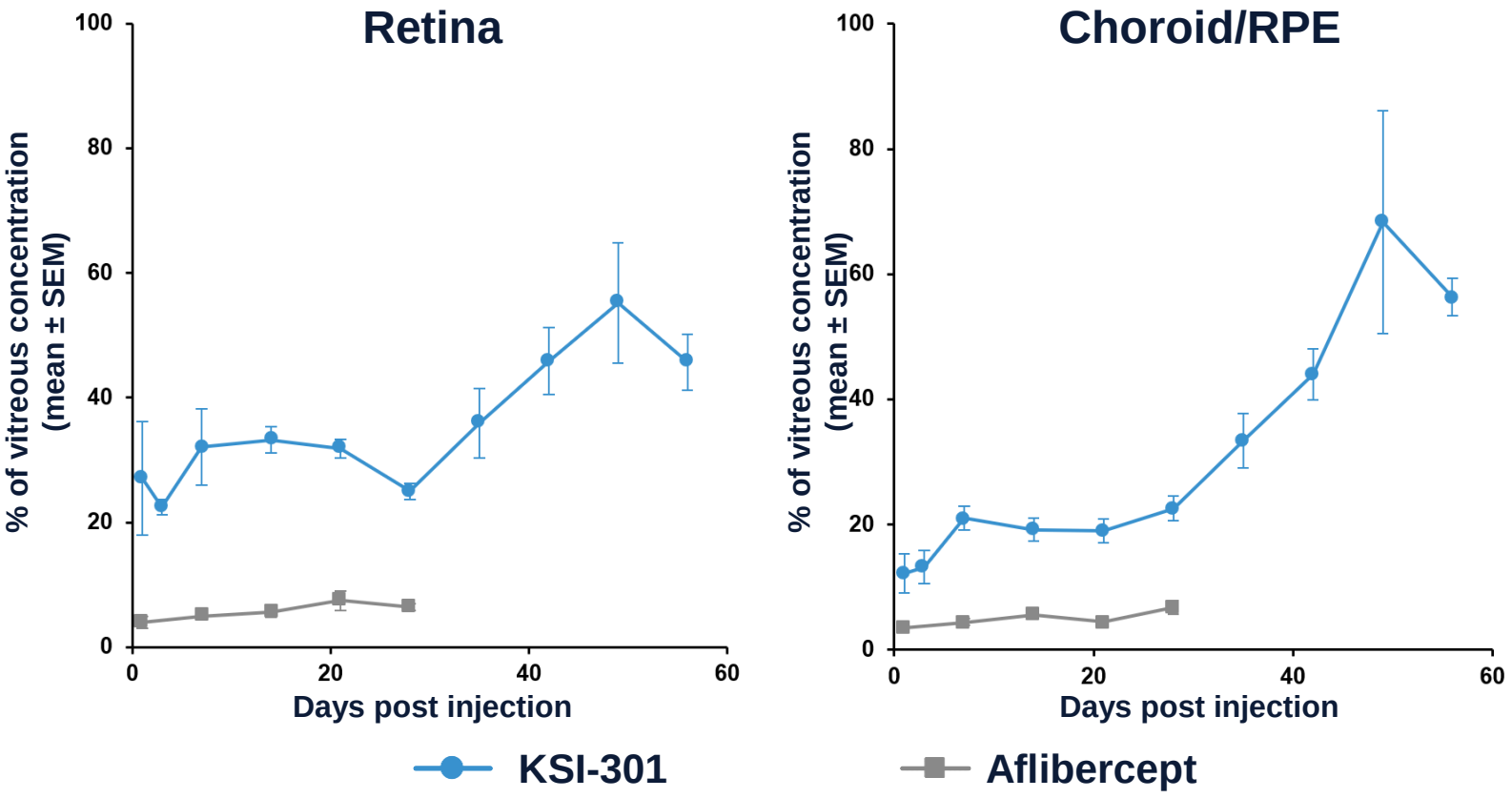


KSI-301 bioconjugate has a deeper potency than other anti-VEGFs and even its unconjugated starting protein

Kodiak data on file

KSI-301 bioconjugate has **greater bioavailability** because of its phosphorylcholine biopolymer

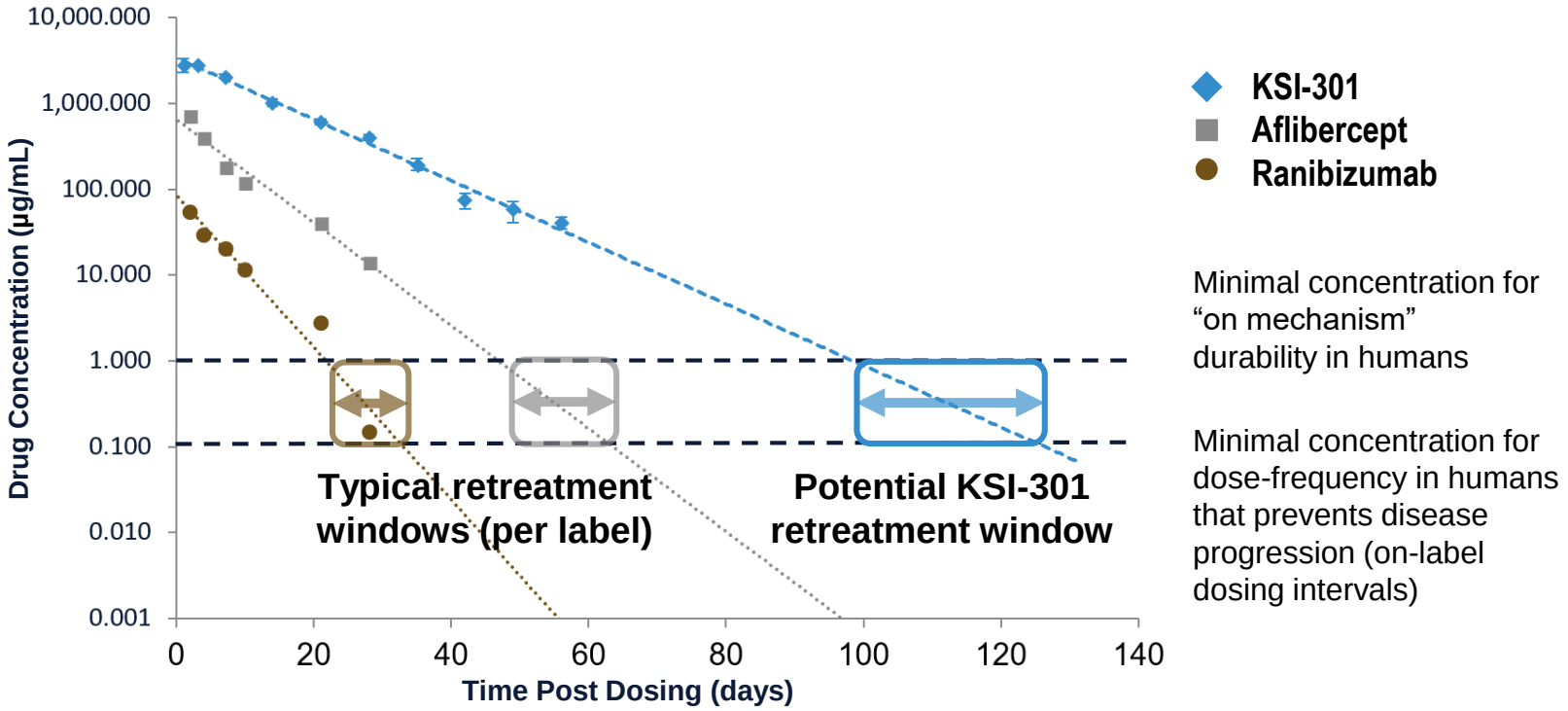
Ocular tissue bioavailability after single intravitreal injection
Data from *in vivo* rabbit models



Covance rabbit ADME (absorption, distribution, metabolism, elimination) model:
Aflibercept data (2008): EVER Congress Portoroz Slovenia Struble (Covance), Koehler-Stec (Regeneron)
KSI-301 data (2017): Struble (Covance), Kodiak
Error bars reflects standard error of the mean

KSI-301 bioconjugate has potential for **extended durability** and **more flexible retreatment window**

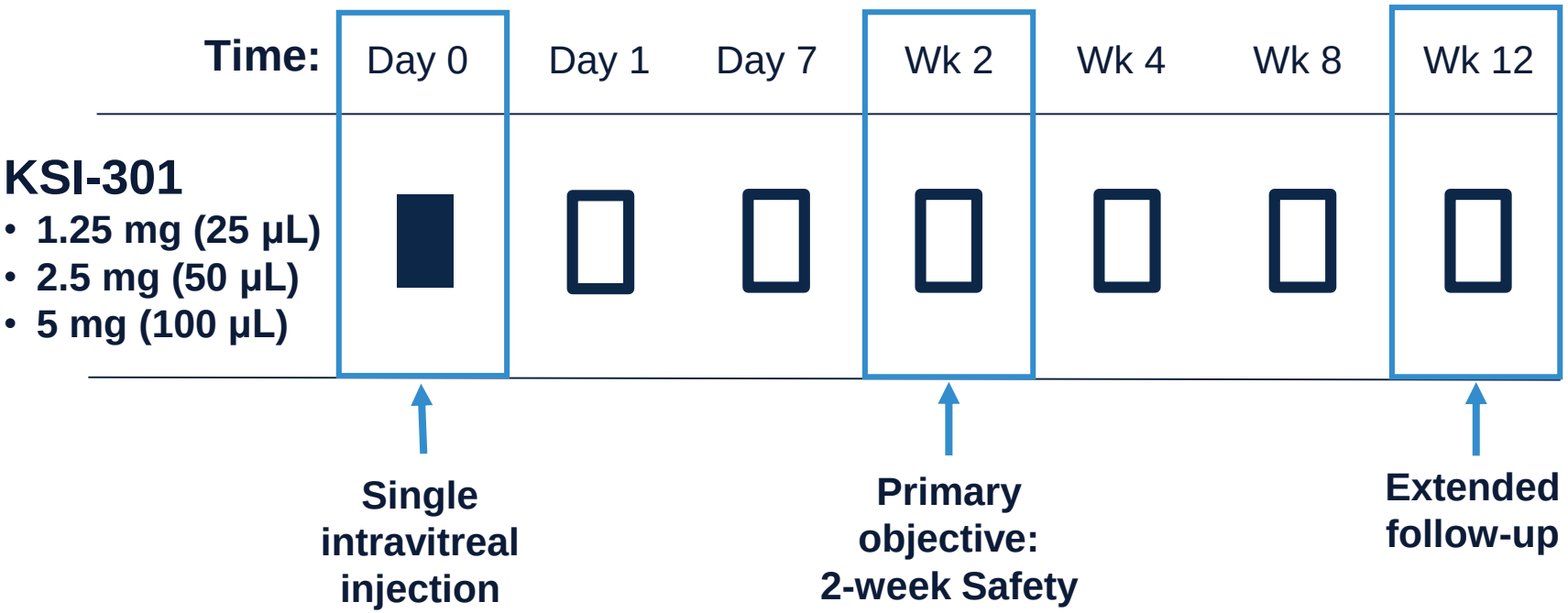
KSI-301 bioconjugate has a flatter (better) ocular PK curve. This translates into multi-Log concentration advantage versus other biologics.



Rabbit *in vivo* PK modeled to human doses and dosing intervals

Lucentis data: Gaudrealt et al (2007) IOVS 46(2) 726 Gaudrealt et al (2007) Retina 27(9) 1260 Bakri et al (2007) Ophthalmol 114(12) 2179
Aflibercept data: EVER Congress Portoroz Slovenia (2008) Struble (Covance) Koehler-Stec (Regeneron). Aflibercept data adjusted arithmetically to reflect 2,000µg dose administered (based on rabbit in vivo dosing of 500 µg).
KSI-301 data adjusted arithmetically to reflect 5,000 µg dose administered (based on rabbit in vivo dosing of 725 µg). Error bars reflects standard error of the mean

KSI-301 Phase 1 clinical study: **single ascending dose** study design



- Eyes with diabetic macular edema (DME), one eye per subject
- 9 subjects – 3 per dosing cohort, 7-day safety review between each cohort
- Conducted at 5 US sites
- Single dose with observation to 12 weeks (no retreatment)

Demographic and ocular **baseline characteristics**

Demographics, n=9	
Age (years, mean)	62
Gender	7M, 2F

Ocular Characteristics, Study Eye, n=9	
Previously received Anti-VEGF	8/9
# of anti-VEGF treatments in last year - median (range)	3 (0, 7)
Time since last anti-VEGF, days - median (range)	95 (52, >365)
IOP, mmHg - mean (SD)	15 (2)
OCT Central Subfield Thickness, microns - mean (SD)	565 (182)
Baseline BCVA, ETDRS letters - mean (SD)	47 (12)
Baseline BCVA, Snellen equivalent	20/100

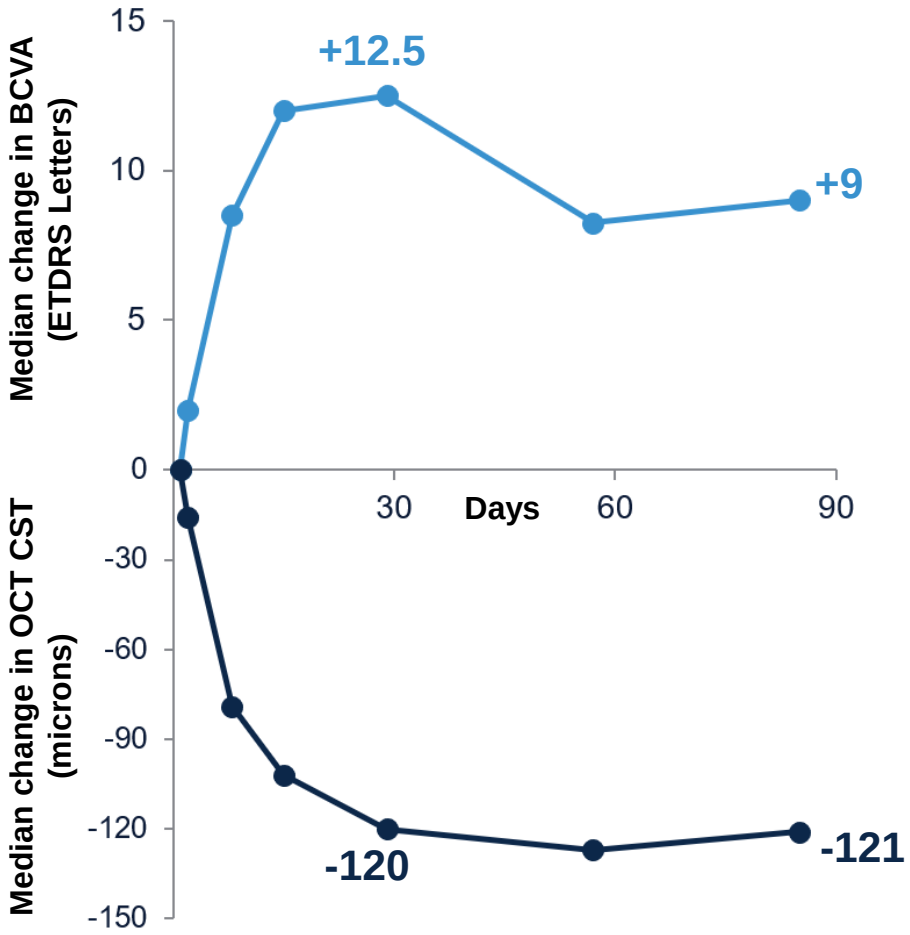
Safety outcomes: **every dose level well-tolerated** through 12 week follow-up period

- No dose limiting toxicities
- No drug-related adverse events or drug-related serious adverse events
- No intraocular inflammation
- Optically clear media after each injection
- No anti-drug antibodies detected in any patient
- Systemic levels 1/3 of bevacizumab C_{max} and 1/6 of D28 level (1.25mg dose)[1]

Number of patients with any AE = 4	N	Serious	Related
Ocular AEs			
Foreign body sensation	1	N	N
Subconjunctival hemorrhage	2	N	N
Floaters (reported in both eyes)	1	N	N
Visual flashes	1	N	N
Non-Ocular AEs			
Fall	1	N	N
Worsening of coronary artery disease	1	Y	N
Swollen feet	1	N	N

1. Avery RL et al. Retina. 2017 Oct;37(10):1847-1858

Improvements in vision and retinal thickness after **single-dose** KSI-301 through 12 weeks



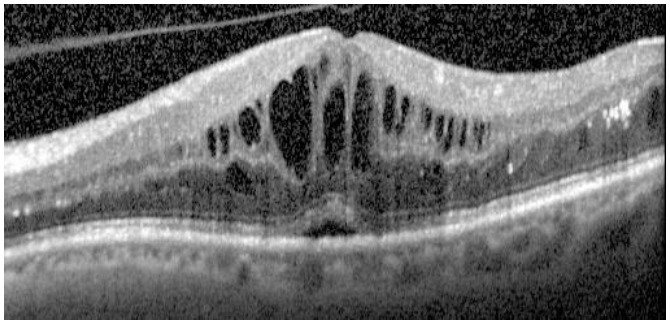
Rapid, high magnitude responses **as early as 1 week** after dosing

Durable improvements out to 12 weeks

Median changes from baseline to week 12
pooled across 3 dose groups (n=9 patients total)

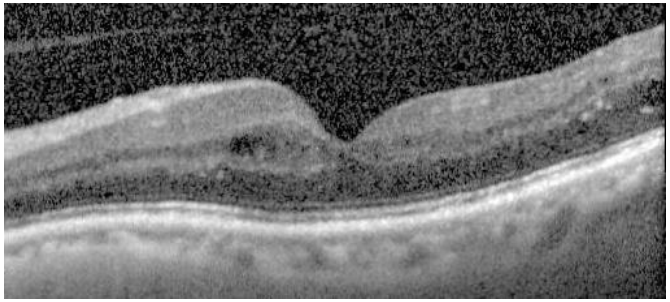
Case example: resolution of macular edema **sustained through 12 weeks** in patient with prior suboptimal response

Baseline

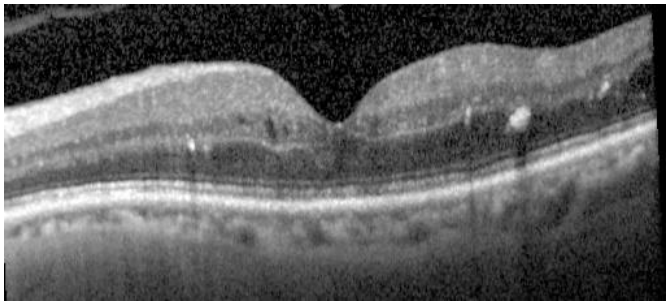


Single dose
KSI-301 (5 mg)

Week 4

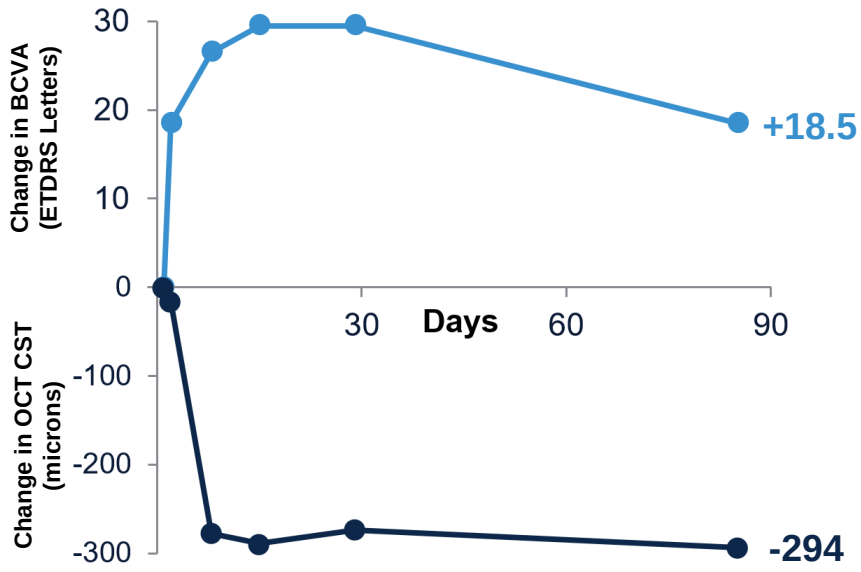


Week 12



Clinical history summary (site reported):

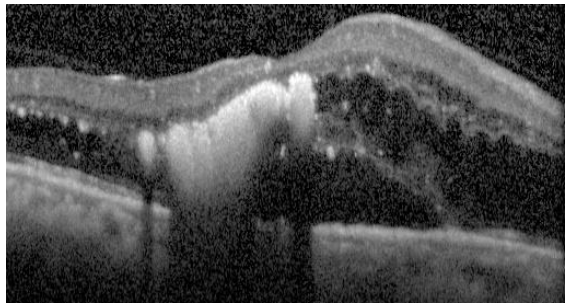
	Date	Treatment	VA Snellen	CST
Retrospective	1/2018		20/40	-
	4/2018	Bevacizumab	20/40	431
	6/2018	Bevacizumab	20/60	655
	8/2018	**KSI-301**	20/160	636



Change from baseline to week 12

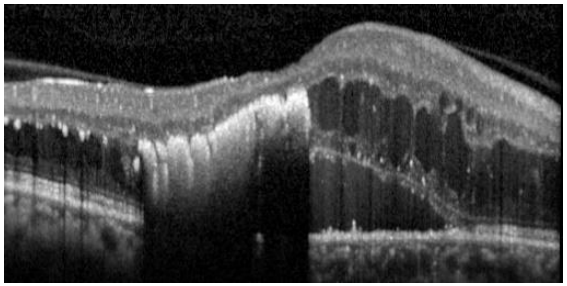
Case example: **improvement through 12 weeks** of subretinal fluid in patient with extensive foveal lipid exudates

Baseline

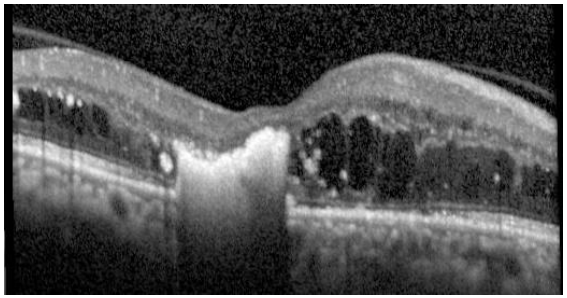


Single dose
KSI-301 (1.25 mg)

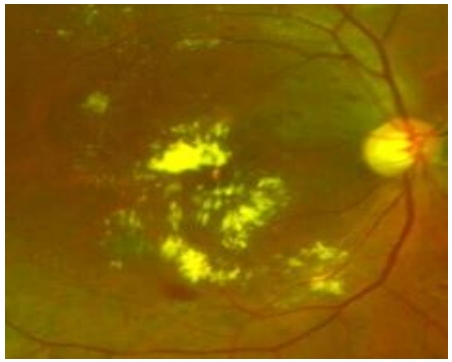
Week 4



Week 12

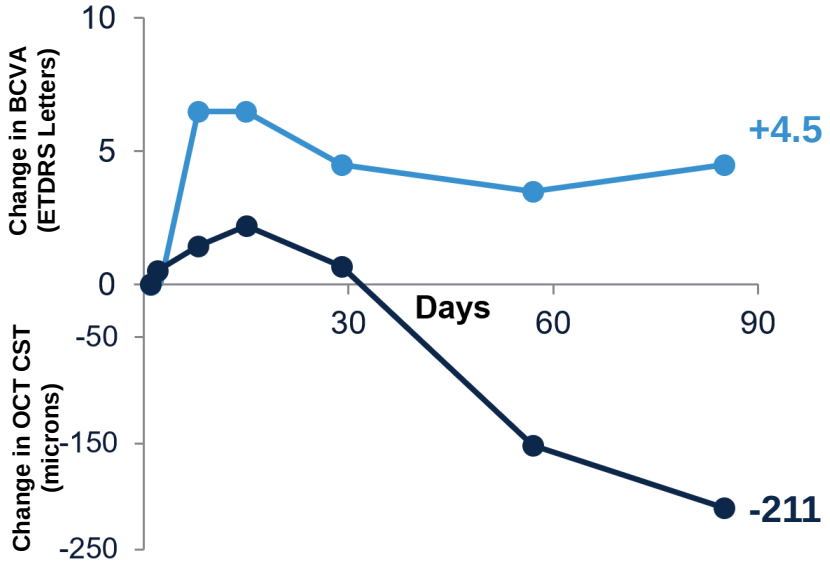


Baseline



Clinical history summary (site reported):

	Date	Treatment	VA Snellen
Retrospective	1/2018	Bevacizumab	20/60
	3/2018	Bevacizumab	20/100
	4/2018	Bevacizumab	20/150
	5/2018		20/350
	7/2018	**KSI-301**	20/80



Change from baseline to week 12

Important early development questions **successfully addressed** in KSI-301 Phase 1 study

✓Manufacturability

✓Optical Clarity

✓Target Tissue Access

✓Safety

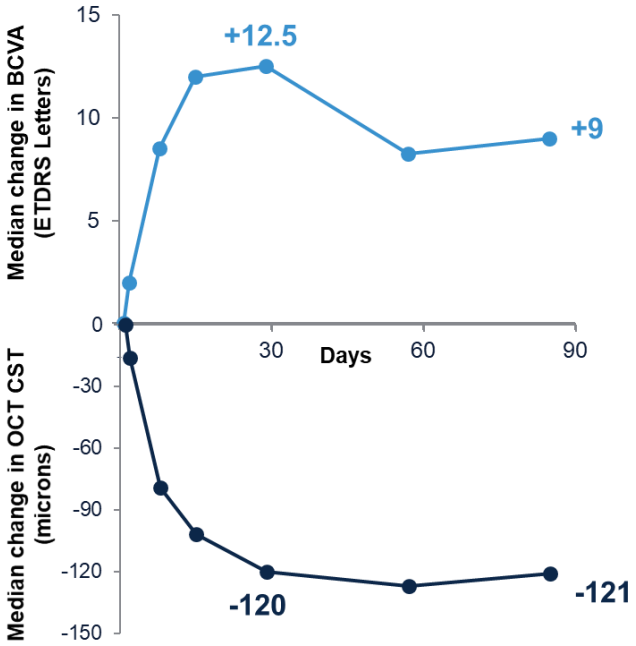
✓Speed of Onset

✓Potency

✓Clinical Durability

Key Takeaways

- **KSI-301** is a novel **Antibody Biopolymer Conjugate** that inhibits VEGF
- Phase 1a single ascending dose study results:
  - Well-tolerated at all dose levels
  - **Rapid-onset, high-magnitude improvements sustained to 12 weeks**
- Objective: the “go-to drug” for induction and maintenance therapy of retinal vascular diseases



- Phase 1b evaluating multiple doses in treatment-naïve wet AMD, DME, and RVO currently enrolling (NCT03790852)
- Phase 2 in treatment-naïve wAMD starting in 2019 with dosing as infrequently as Q20W and all patients ≥Q12W
- Additional studies in DME, NPDR in planning
- Dedicated China pivotal programs in planning

Acknowledgements

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- **Ocular Imaging Research and Reading Center**

Appendix

Phase 1b open-label study in wet AMD, DME and RVO

											Primary Endpoint
Week		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**
KSI-301 5 or 2.5 mg	**wAMD**	■	■	■	□	□	□	□	□	□	
	DME/ DR	■	■	■	□	□	□	□	□	□	
	RVO	■	■	■	□	□	□	□	□	□	

■ = KSI-301 injection

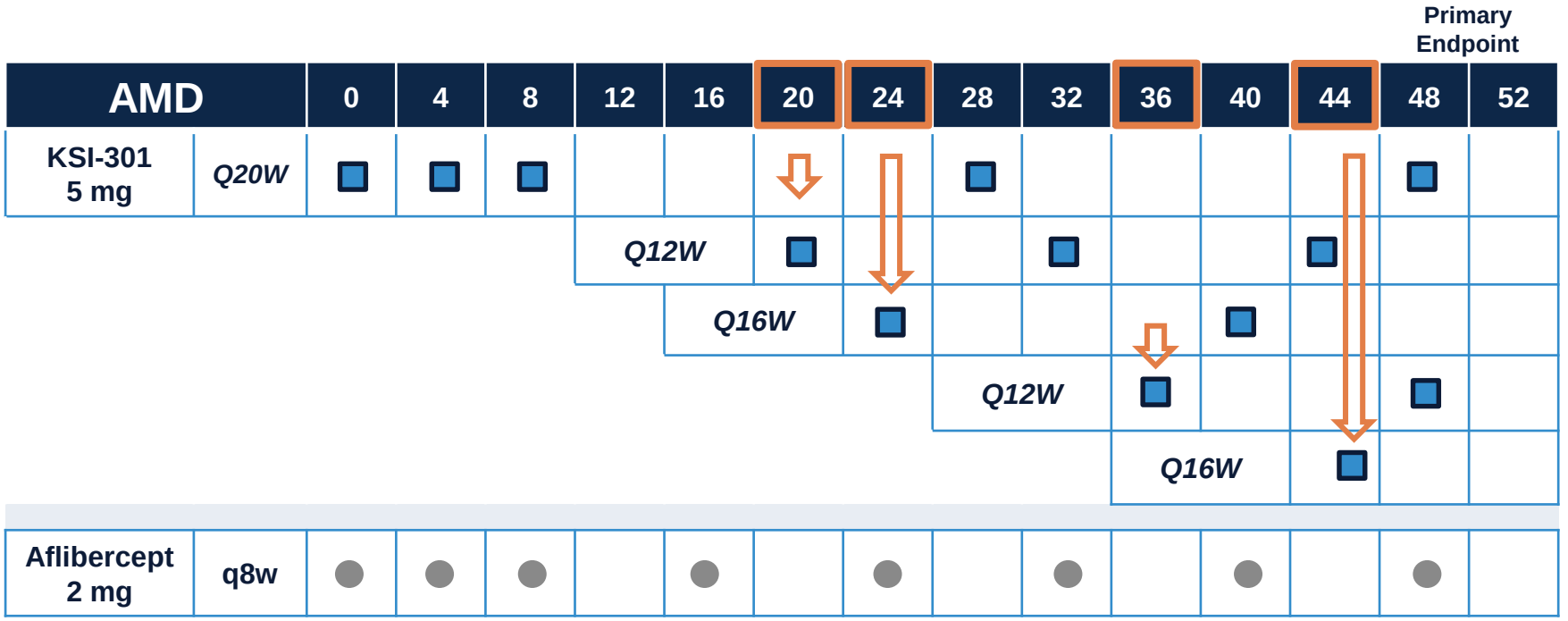
□ = Dosing as needed (PRN)

□ = Retreatment criteria assessment

- **Study now recruiting** (NCT03790852)
- Open-label study to further explore KSI-301 safety, bioactivity, durability (~50 patients)
- Anti-VEGF treatment naïve patients only
- 3 loading doses followed by indication-specific re-evaluation and retreatment criteria
- OCT Angiography to generate novel data for “on mechanism” durability

Phase 2 study in wet AMD (US/EU)

Pivotal study design, head-to-head against standard of care aflibercept



= KSI-301 injection

= Aflibercept injection

= Disease Activity Assessment Visit

= Disease Activity Dosing Adjustment

- **All patients ≥Q12W with KSI-301**
- **As infrequent as Q20W dosing with KSI-301**
- Non-inferiority pivotal design study
- Estimated ~400 patients (US/EU)
- On track to begin enrolling in 2Q 2019, with interim and primary readouts in 2020 and 2021